Editorial

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A novel strategy employing the flavonoid fisetin to halt the progression of renal fibrosis in obstructive nephropathy

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Ureteral obstruction (UO) has a significant impact on renal function by altering hemodynamics, decreasing glomerular filtration, and inducing renal transcriptomic and metabolomic changes. It can also cause structural changes in the kidney parenchyma, most notably hydronephrosis and renal fibrosis. Renal fibrosis, a common feature of chronic kidney disease (CKD), is a complex process characterized by loss of capillary networks, progressive accumulation of fibrous collagens, and activation of myofibroblasts and inflammatory cells. The process results in a substantial decline in renal blood flow and tissue perfusion, impaired tubular handling of water and electrolytes, and an increase in urinary protein excretion. CKD can be caused by many diseases, including diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, chronic obstructive nephropathy, and others. Globally, the prevalence of CKD is increasing, which poses a significant clinical challenge as CKD can progress to end-stage renal disease (ESRD), which requires dialysis and kidney transplantation. Approximately 9.1% of the world's population, or 700 million individuals, have CKD.

Chronic obstruction of the urinary tract and urine flow leads to obstructive nephropathy and ESRD. Animal models have contributed significantly to the comprehension of the mechanisms underlying structural and functional alterations. In particular, various species with unilateral UO (UUO), a model for experimental hydronephrosis, have revealed novel mechanisms underlying renal fibrosis. However, animal models of complete and irreversible UO, such as UUO, have limitations for examining tubule damage as well as hemodynamic alterations, as the majority of clinical UO in human patients involves partial and chronic UO as opposed to acute and completely irreversible UO.

The pathogenesis of fibrosis is an imbalance between the synthesis, deposition, and degradation of the extracellular matrix. Diverse molecular mechanisms are involved, including growth factors (transforming growth factor-β [TGF-β], platelet-derived growth factor, connective tissue growth factor), endothelin-1, and integrins. Among profibrotic molecules, TGF-β is critical for cell growth, differentiation, proliferation, apoptosis, immune response, and fibrosis. TGF-β promotes fibrosis by both canonical and non-canonical pathways. TGF-β1 binds to TβRII, which activates TβRI by phosphorylation, thereby activating TGF-β1 downstream effectors. Suppressor of mothers against decapentaplegic (Smad) is associated with the canonical pathway. TGF-β1 signaling transduction occurs via the receptor-regulated Smads (R-Smads), e.g., Smad2 and Smad3, both of which are overexpressed in human fibrotic

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kidneys [1]. Phosphorylated Smad2 and Smad3 complexes with Smad4 translocate into the nucleus and modulate the transcription of profibrotic genes, such as collagen I and III. Inhibiting Smad2 in kidney cells (Smad2 knockouts are embryonically lethal) exacerbates fibrosis. In contrast, mice lacking the Smad3 gene exhibit slower progression of renal fibrosis, indicating that Smad2 and Smad3 function in opposition in the progression of renal fibrosis [2]. The non-canonical Smad-independent signaling pathways include mitogen-activated protein kinase (MAPK), Jun N-terminal kinases, Rho-like GTPase, and PI3k/AKT. These pathways influence the transcription of target genes that induce an epithelial-to-mesenchymal transition (EMT) or apoptosis [3].

As treatment strategies for CKD after the development of tubulointerstitial fibrosis are ineffective, researchers should instead focus on elucidating the early disease process. Treatments typically involve reducing the production of fibrotic and inflammatory proteins, suppressing fibroblast proliferation, preventing EMT, reducing oxidative stress, inhibiting the action of nuclear factor κB (NF-κB), reducing the phosphorylation of Smad2/3 or MAPKs, correcting metabolic acidosis, and inhibiting the activation of the renin-angiotensin system. Fig. 1 provides examples of potential therapeutic targets for inhibiting renal fibrosis progression in CKD [4,5].

In the current issue of *Kidney Res Clin Pract*, Ju et al. [6] reported that treatment with fisetin (3,3′,4′,7-tetrahydroxyflavone), a flavonol found in smoketree (*Cotinus coggygria*) and various fruits and vegetables (e.g., strawberry, apple, grape, persimmon, cucumber, and onion at concentrations in the range of 2–160 μg/g) inhibited the progression of renal fibrosis in the kidneys of C57BL/6 female mice subjected to UUO for 7 days. The proposed mechanisms were inhibition of phosphorylation of Smad3, oxidative damage, inflammation, apoptotic cell death, and decreasing the accumulation of profibrotic M2 macrophages in the obstructed kidneys. Intraperitoneal injections of fisetin (25 mg/kg) were administered one hour prior to surgery and every other day for seven days following surgery. In addition, pretreatment with fisetin (40 μM) substantially decreased the TGF-β1–induced phosphorylation of Smad2 and Smad3 in HK-2 cells, the human proximal tubular cell line. Due to their potential therapeutic pharmacological

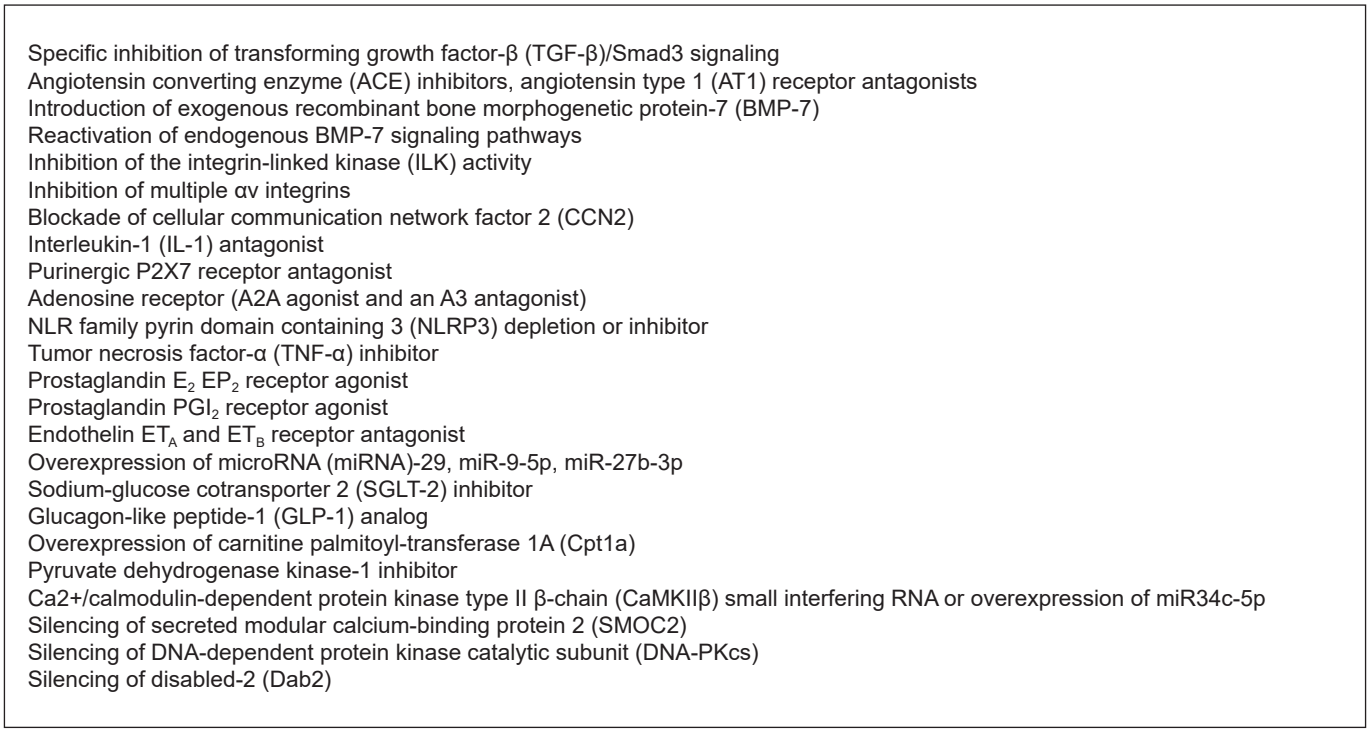

Figure 1. Potential therapeutics for the inhibition of renal fibrosis (based on findings from animal studies).

properties, flavonoids have received considerable attention as pharmaceuticals and health food supplements. Antioxidant, anti-inflammatory, and antineoplastic actions are some of the biological functions attributed to fisetin. Sahu et al. [7] used a cisplatin-induced nephrotoxicity model to show that fisetin protects kidney function by reducing oxidative stress, restoring mitochondrial respiratory enzyme activities, decreasing apoptosis in renal tubular cells, and inhibiting NF-κB activation. Moreover, fisetin improves renal fibrosis in the hyperuricemic nephropathy model, as shown by Ren et al. [8] via modulation of STAT3 and TGF-β1/Smad3 signaling.

Based on their chemical structure, flavonoids can be classified into flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins and chalcones. Fisetin, the most prevalent bioactive flavonol, exerts a variety of biological effects, including anti-inflammatory properties and decreases in oxidative stress and apoptotic cell death [9]. Fisetin forms complexes with Al(III), Cu(II), Zn(II), and Pb(II) at its ligand chelation sites (3-hydroxy-4-Oxo and 3',4'-dihydroxy group). Due to its ability to accept free radicals, it was hypothesized that the association of flavonoids with a metal ion would enhance their biological activity. In addition, it was demonstrated that metal complexation promotes the antioxidant properties of flavonoids.

An acute oral toxicity study revealed that the complex has an lethal dose 50% of 500 mg/kg; however, there were no treatment-related alterations in hematological and serum biochemical parameters in the 50, 100, and 200 mg/kg groups [10]. Interestingly, a previous study showed moderate infiltration of inflammatory cells in the kidney tissues of rats administered 2.5 mg/kg fisetin intraperitoneally [6]. In the current issue, however, Ju et al. [6] employed intraperitoneal injections of fisetin (25 mg/kg) in mice, where the number of F4/80-positive cells in the kidneys was comparable between vehicle-treated control mice and fisetin-treated control mice. Further studies are needed to examine the dose-dependent response in the kidney.

There is evidence that fisetin has anti-inflammatory, anti-neoplastic, and antioxidant properties. More *in vitro* and *in vivo* research is needed to confirm that fisetin has renoprotective effects and to determine the precise molecular mechanisms by which it slows the progression of CKD, including obstructive nephropathy. Patients with renal disease, especially those at a more advanced stage of renal fibrosis or CKD, have rarely been cured by single-agent-targeted therapies. There is a need for additional research into target identification and pathway analysis.

Conflicts of interest

The author has no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

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